GENECHOC Study

Identification of genetic markers modulating the arrhythmic risk in patients with severe cardiopathy

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Introduction Sudden cardiac death (SCD) prevention is a major issue in heart failure. A familial predisposition is known suggesting important role of genetic factors in arhythmic risk.

Objectives Identifying genetic markers modulating the arrhythmic risk.

Methods We included patients with a cardioverter defibrillator in primary prevention for a severe cardiopathy in 22 french centers between 2009 and 2017. Patients were followed during 72 months and divided into 2 groups : cases with an arrhythmic event during follow-up and controls. A global wide association study (GWAS) was done. Single Nucleotid Polymorphism (SNP) genotyping was performed on Affymetrix Axiom Precision Medicine Research Array plates. Fluorescence intensities were quantified using the Affymetrix GeneTitan Multi-Channel Instrument, and primary analysis was conducted with Affymetrix Power Tools. Genotype calling was performed using the 'apt' program. A total of 239,994 markers were available for analysis.

Results The GWAS analysis was conducted on 332 cases and 567 controls. To complement the directly genotyped SNPs we performed large-scale imputation based on the Haplotype Reference Consortium European ancestry panel leading do a dataset of 7.5 million of SNPs. No locus shows genome-wide significant association ($P<5\times10-8$). However several signals with a nominal p-value ($5\times10-8<$ p-value $<5\times10-5$) and supported by more than 2 SNPs in high linkage desequilibrium point to suggestive genes and pathways. Signals indicate correlation with variants or genes previously associated with ECG parameters and cardiac diseases. Variants identified point to regulatory regions of the genome and may then propose a molecular mechanism predisposing patients to arrhythmias.

Conclusion No locus raises genome-wide significance but several signals point to interesting genes and pathways.To increase the power of the analysis, cases and controls will be compared to a large cohort from the general population. A replication study will also be done in a cohort of patients with a less severe cardiopathy but who have done an arrhythmic event anyway.

We thank Genomic and Bioinfomatic Nantes infrastructures (GenoBiRD, Biogenouest) for their contribution to this project.